

Sandostatin LAR in Acromegalic Patients: Long Term Treatment

ANETTE KVISTBORG FLØGSTAD*, JOHAN HALSE, SØREN BAKKE,
IOANA LANCRANJAN, P. MARBACH, CH. BRUNS, AND JAK JERVELL

*Section of Endocrinology, Medical Department B (A.K.F., J.H., J.J.) and Department of
Neuroradiology (S.B.), Rikshospitalet, University of Oslo, Oslo, Norway; and Sandoz Pharma Ltd.
(I.L., P.M., C.B.), Basel, Switzerland*

ABSTRACT

We have evaluated the long term effects and safety of Sandostatin LAR, a long acting formulation of octreotide, during 18 subsequent injections given every fourth week to 14 octreotide-sensitive acromegalic patients. The dosages (20, 30, or 40 mg) were adjusted according to GH response, side-effects, or symptom relief and assessed on day 28 after each injection. We found a stable and consistent suppression of GH and insulin-like growth factor (IGF-I) during the entire study period. Daily mean GH levels were suppressed below 2 $\mu\text{g/L}$ in 9, to between 2–5 $\mu\text{g/L}$ in 3, and to between 5–10 $\mu\text{g/L}$ in 2 patients. The corresponding IGF-I values were suppressed to below 500 $\mu\text{g/L}$ in 9 patients and to between 500–1000 $\mu\text{g/L}$ in the remaining 5 patients. Increasing the dosage of Sandostatin LAR from 20 to 30 mg had no obvious additional effect on GH suppression, but provided a further

decrease in IGF-I levels. Forty milligrams of the drug had no additional effect on GH or IGF-I compared to 30 mg. Acromegalic signs and symptoms improved during treatment. Although the fluctuations of daily mean octreotide levels were high, dosage increments caused an increase in the average serum concentration in the individual patient. Pituitary tumor size reduction was seen in all previously untreated patients ($n = 4$). We found only minor changes in glucose metabolism (oral glucose tolerance test and hemoglobin A_{1c}) during treatment, but no biologically relevant changes in thyroid function (TSH, T₃, and free T₄). One patient developed asymptomatic gallstones, and another acquired vitamin B12 deficiency during treatment. The drug is well tolerated during long term treatment. Sandostatin LAR may well be the future medical treatment of choice for acromegalic patients. (*J Clin Endocrinol Metab* 81: 23–28, 1997)

TREATMENT with octreotide has become the preferred medical treatment for acromegaly (1–3). We have demonstrated that Sandostatin LAR, the slow release formulation of octreotide, reduces GH and insulin-like growth factor I (IGF-I) levels similar to octreotide given as sc injections three times daily in acromegalic patients (4). Tumor size shrinkage by 20–100% during long term sc treatment with octreotide has been reported (1–3, 5–11). There has been only one previous report, comprising only eight patients treated for up to 1 yr, on the long term effects of Sandostatin LAR (12). The purpose of the present study was to determine the optimal dosage; the effects on GH, IGF-I, and tumor size; as well as the safety and tolerability of Sandostatin LAR during long term treatment of acromegaly.

Subjects and Methods

Fourteen acromegalic patients were included in the study. All had elevated basal GH levels that were not suppressed below 2 $\mu\text{g/L}$ during an oral glucose tolerance test and elevated IGF-I levels. A pituitary tumor was demonstrated by computed axial tomographic (CT) scan in all patients. None of the patients had hypersecretion of other pituitary hormones (FSH, LH, ACTH, PRL, or TSH). None had received bromocriptine treatment for acromegaly within 1 month before the study. Each patient gave their written informed consent to participate in the

study, which was approved by the hospital drug committee, the regional ethical committee, and Norwegian Medicines Control Authority.

The patients (Table 1; eight women and six men) had a median age of 52 yr (range, 27–69 yr), a median weight of 76.3 kg (range, 45.0–117.0 kg), a median height of 173.3 cm (range, 155.5–192.0 cm), and a median duration of acromegaly from time of diagnosis of 4.8 yr (range, 0.3–20 yr). Four patients were newly diagnosed acromegalics. Ten had undergone either pituitary surgery and/or external pituitary irradiation, six had received bromocriptine, and one patient had received long term treatment with octreotide. All patients were good responders (suppression of mean GH to 50% of basal levels and/or to $<5 \mu\text{g/L}$) to octreotide (100 or 200 μg) given sc three times daily and had previously received either a single (20 or 30 mg) or two (3, 6, 9, or 12 mg and 20 or 30 mg) injections of Sandostatin LAR im in a dose-response study (4).

In this, still ongoing, open study Sandostatin LAR was given as im injections every 4 weeks, and this report comprises the results of a total of 18 injections. Initially, all participants received either 20- or 30-mg injections for a total of six injections. The dosage was adjusted individually, according to GH response (a mean GH value of $<2 \mu\text{g/L}$ on study days was considered adequate), side-effects, or inadequate symptom relief. In subjects not optimally treated with 30 mg, injections of 40 mg Sandostatin LAR were attempted from the seventh injection on.

The baseline GH (means of 12 hourly obtained GH values between 0800–2000 h) and IGF-I (means of IGF-I values obtained at 0800–0900 h) values obtained during the dose-range study (4) were also used as baseline values in the present study. During the present study the patients were evaluated on the 28th day after every im injection of Sandostatin LAR. Assessments of 8-h (hourly between 0800–1600 h) GH and octreotide profiles (hourly for the first six injections, only two samples at 0800 and 0900 h thereafter) and IGF-I measurements (two samples at 0800 and 0900 h), as well as registration of adverse events and acromegaly-related signs and symptoms were performed on all study days. Acromegaly-related signs and symptoms (headache, fatigue, perspiration, paresthesia, joint pains, and carpal tunnel syndrome) were rated on a 5-point scale (0, absent; 1, mild; 2, moderate; 3, severe but not incapacitating; 4, severe and incapacitating). Physical examination and standard laboratory analysis were performed at baseline and after every sixth injection. Echographic examination of the gallbladder and biliary

Received March 22, 1996. Revision received July 31, 1996. Accepted August 5, 1996.

Address all correspondence and requests for reprints to: Dr. Anette Kvistborg Fløgstad, Section of Endocrinology, Medical Department B, Rikshospitalet, 0027 Oslo, Norway.

* Recipient of a grant from the Norwegian Research Council for Science and Humanities.

TABLE 1. Patients' characteristics

Patient no. (age/sex) (yr/F,M)	Time since diagnosis of acromegaly (yr)	Previous treatment
1 (57/F)	6	Radioth, Bromo
2 (36/M)	1.5	Surgery
3 (60/F)	6	Surgery
4 (39/F)	3.5	Surgery ×2, Octr
5 (42/F)	1	Surgery
6 (27/F)	7	Surgery, Bromo
7 (69/M)	17	Surgery, Bromo
8 (63/M)	20	Surgery, Radioth, Bromo
9 (59/M)	19	Surgery, Bromo
10 (58/F)	10	Surgery
11 (51/M)	0.3	None
12 (42/F)	0.3	None
13 (36/F)	0.3	None
14 (53/M)	0.3	None

Radioth, Radiotherapy; Bromo, bromocriptine; Octr, octreotide, sc; Surgery, transsphenoidal/subfrontal adenectomy; None, no previous treatment, except for 4 weeks treatment with Sandostatin (300–600 mg, sc, daily).

system and measurements of glycosylated hemoglobin A_{1C} (HbA_{1C}), TSH, T₃, and free T₄ were performed at baseline and after every third injection.

Oral glucose tolerance tests were performed before the start of the study and after the 12th and 18th injections of Sandostatin LAR. CT or magnetic resonance imaging (MRI) scan of the pituitary gland was performed at baseline and after every sixth injection. Standardized meals were served on all study days at 1000 and 1300 h.

IGF-I levels were measured by RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA; normal range, 65–500 µg/L), GH was determined by a double monoclonal antibody technique (Delfia Kit, Wallac OY, Turku, Finland), and octreotide concentrations were measured by RIA (Biopharmaceutical Department, Drug Safety Assessment of Sandoz Pharma, Basel, Switzerland), as previously described (4, 13). Insulin and C peptide levels were measured by RIAs (Diagnostic Product Corp., Los Angeles, CA).

Standard methods were used for assessment of clinical chemistry parameters. CT scans of the pituitary were performed with the patient in the coronal position after bolus contrast injection (100 mL; Omnipaque 300, Nycomed, Oslo, Norway) using a Somatom DR (Siemens, Erlangen, Germany). Tumor size was estimated from continuous 2-mm scans through the pituitary region. Sagittal and coronal T1 weighted (TR 600/TE 20) MRI scans of the pituitary tumor were obtained without, and in most patients also with, contrast injection (Magnevist, Schering, Berlin, Germany) using a Siemens Magnetom 63, (Siemens, Erlangen, Germany). The scan parameters were 3 mm slices/0.3 mm distance. The greatest length, height, and width (in centimeters) of the pituitary tumor were measured, and the product of these measurements was considered an index of tumor size (in cubic centimeters). No attempt was made to correct for irregularities in tumor shape when estimating this index. Because this study is still ongoing, the results for tumor size assessments after 24 months are included.

Data analysis

The GH, IGF-I, and octreotide data determined on each profile day are presented for each individual as a daily mean. A *t* test or a paired *t* test was used for testing statistical significance between groups. For correlation analysis, a Spearman rank order test was used. *P* < 0.05 was considered significant.

Results

GH

The effect of Sandostatin LAR on daily mean GH levels during all study days (Fig. 1) and as an average for the entire

study period (Fig. 2) for each patient are presented. During the entire study period, daily means of GH were, on the average, suppressed below 2 µg/L in nine, to between 2–5 µg/L in three, and to between 5–10 µg/L in two patients. GH was stable and consistently suppressed during the treatment period (Fig. 3), except in one patient, whose mean daily GH varied from 4–10 µg/L. The standard deviations in mean GH (mean of the daily average GH) for each study subject varied between 0.1–0.8 µg/L.

Twenty, 30, and 40 mg Sandostatin LAR suppressed mean GH levels compared to basal values (Table 2). However, in the individual patient, the increment of the dosage of Sandostatin LAR to above 20 mg was not associated with improved suppression of GH (Table 2). There was a positive correlation between mean GH and mean IGF-I levels both pretreatment (*r* = 0.64; *P* = 0.015) and during treatment with Sandostatin LAR im (*r* = 0.64, *P* = 0.015).

IGF-I

The effect of Sandostatin LAR on daily mean IGF-I levels during all study days (Fig. 1) and the average during the entire study period (Fig. 2) for the individual patients are presented. Daily means of IGF-I were, on the average, suppressed to below 500 µg/L (normal range) in nine patients and to between 500–1000 µg/L in the remaining five patients. Except for one patient, who showed a gradual decrease in mean daily IGF-I from 1049 to 681 µg/L, which was not associated a concomitant GH reduction, the intrasubject fluctuation in daily mean IGF-I during treatment, was low. The individual sds for mean IGF-I (mean of the daily mean IGF-I values) varied between 30–100 µg/L (Fig. 3). Twenty, 30, and 40 mg Sandostatin LAR suppressed IGF-I compared to basal values (Table 2). Although an increase of dosage from 20 to 30 mg was associated with a decline in IGF-I, a further increase to 40 mg was not (Table 2).

Octreotide

Mean serum octreotide concentrations after injection of the different doses of Sandostatin LAR are shown in Table 2. Daily mean octreotide levels fluctuated both in the individual patient and among the patients after injection of similar dosages. Individual sds for mean octreotide (mean of the daily mean octreotide) varied between 231–2333 ng/L (17–72% of the mean octreotide levels). Increasing the dosage of Sandostatin LAR caused an increase in the average serum concentration in the individual patient (Table 2).

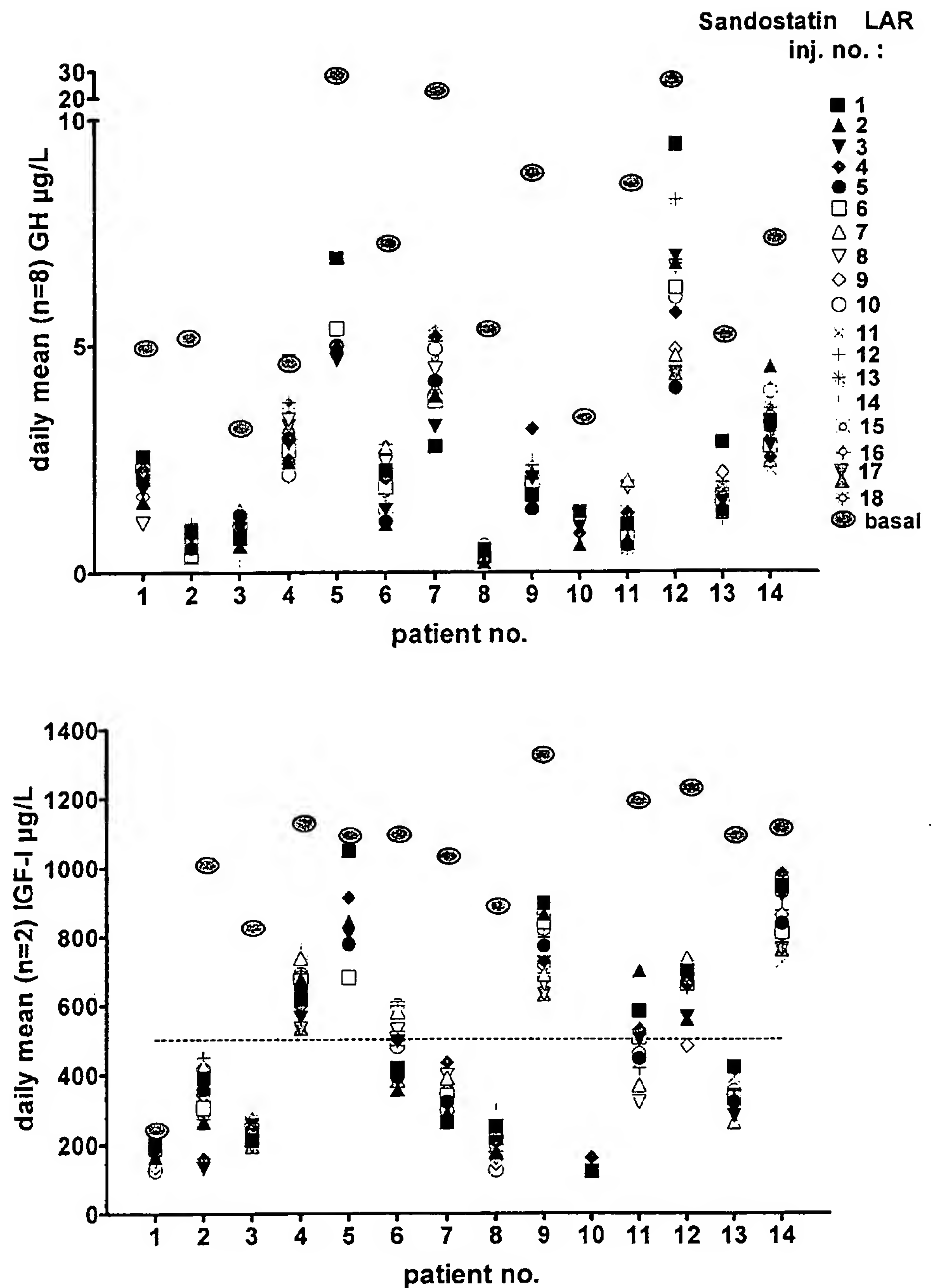
Clinical evaluation

Regardless of the dosage administered, the acromegalic sign and symptom score improved during im treatment with Sandostatin LAR (Table 2). Neither GH, IGF-I, nor serum octreotide levels correlated with the symptom score or the improvement in symptom score during treatment.

Tumor size

A greater than 20% reduction in tumor size was seen in the four previously untreated patients (Fig. 4). In two of these, tumor size reduction was gradual and continuous through-

FIG. 1. GH concentrations (micrograms per L) in each patient, expressed as the daily mean of 8 samples taken hourly, and IGF-I concentrations (micrograms per L) in each patient, expressed as the daily mean of 2 samples (taken at 0800 and 0900 h), on day 28 after 28 subsequent injections of Sandostatin LAR. The injection number is identified by different symbols. The upper normal range of IGF-I is identified by a dotted line.



out the treatment period, whereas the other two patients responded with a major tumor reduction within the first 6 months of treatment. Of the previously treated patients, three had no visual residual tumor, and seven showed no definitive tumor shrinkage.

Tolerability

Three patients discontinued study medication prematurely. One patient (no. 1) had a cerebral infarction after 11 injections. She had a history of breast cancer and hypertension and was a heavy smoker. Another patient discontinued the study in preference for a second pituitary operation after

six injections (patient 5). The third patient discontinued study due to gastrointestinal complaint and loss of scalp hair after four injections (patient 10). Transient hair loss during Sandostatin LAR treatment was also experienced by another patient (patient 8).

One patient taking 0.1 mg T_4 daily experienced a single episode of atrial fibrillation after alcohol intake. One patient developed gallstones during treatment. He has slightly elevated alkaline phosphatase, but is asymptomatic and continues treatment with Sandostatin LAR. Dilatation of the gallbladder and/or biliary ducts (2 patients) and sludge in the gallbladder (1 patient) were found on ultrasound exam-

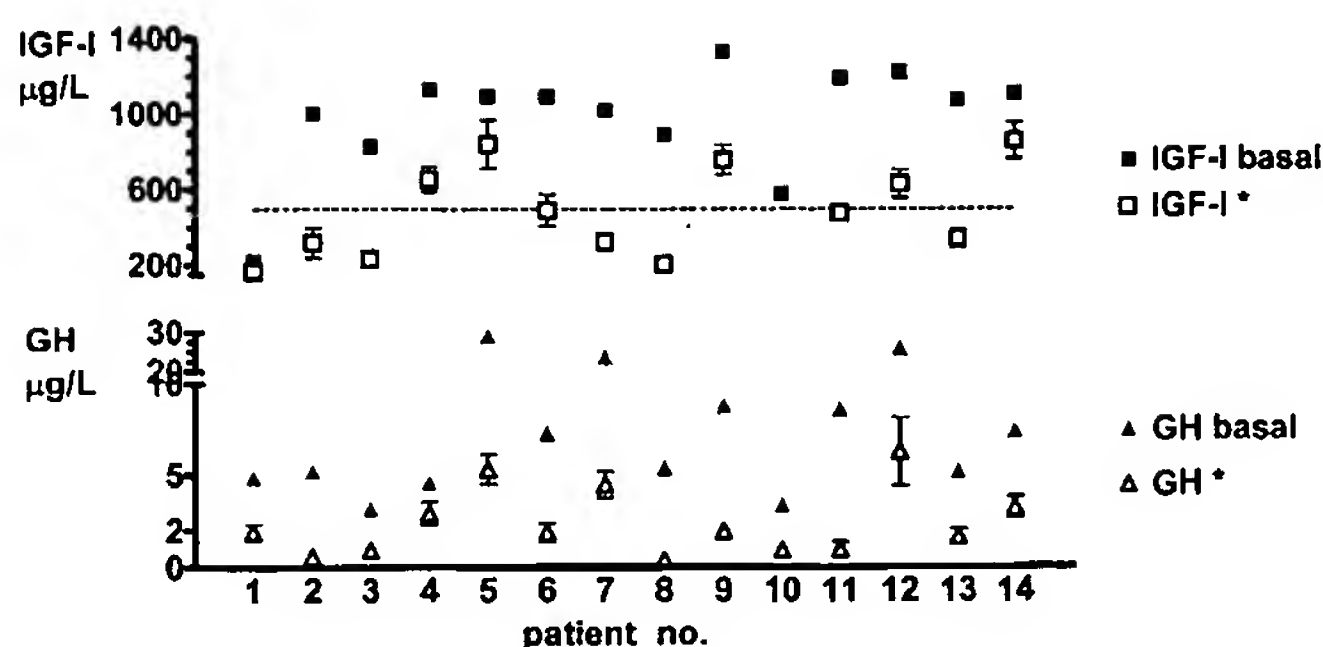


FIG. 2. Individual daily mean of GH and IGF-I pretreatment (basal) and mean \pm SD on day 28 during 18 subsequent injections of Sandostatin Lar (*). Upper normal range for IGF-I is identified by a dotted line.

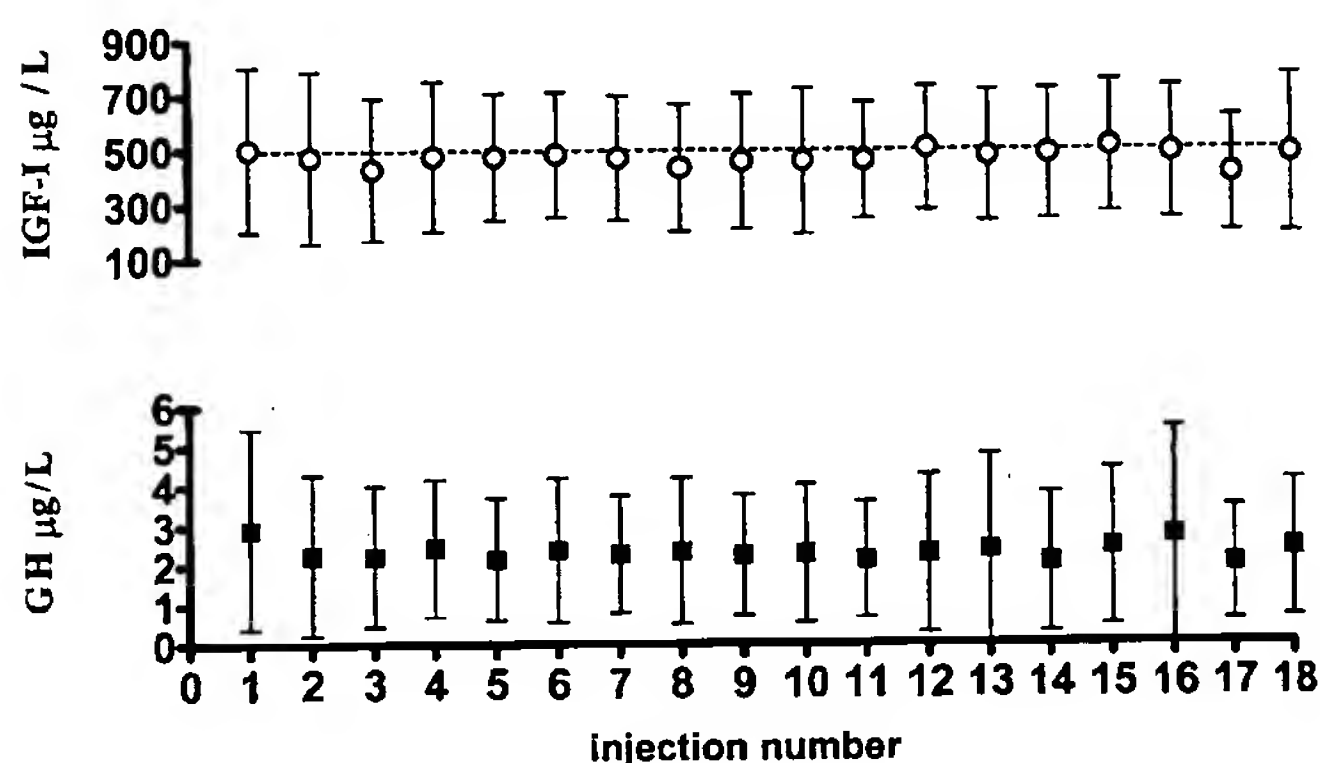


FIG. 3. GH and IGF-I concentrations, expressed as mean ($n = 14$) and standard deviations, measured on day 28 after each of 18 subsequent injections of Sandostatin Lar im. Upper normal range for IGF-I is identified by a dotted line.

ination during treatment. In all 3 patients, the last echographic examination was described as normal. An additional 3 patients had polypoid lesions in the gallbladder at inclusion that did not progress during treatment. The remaining 8 patients had normal echographic examinations of both gallbladder and bile ducts. Intermittent, mild to moderate gastrointestinal complaints, most commonly loose stools and flatulence, were reported by 12 of the 14 patients during the first 6 months of treatment and by 8 of the 12 patients during the last 12 months of treatment. One patient acquired anemia and vitamin B12 deficiency during treatment with Sandostatin LAR. Gastroscopy revealed no abnormality, and parietal cell antibodies were not found. Since then, the patient has received substitution treatment with vitamin B12, and hemoglobin levels are within the normal range. Evaluation of TSH, total and free T_4 , and T_3 serum concentrations in the remaining patients did not reveal any impairment of thyroid function (mean \pm SD of TSH varied between 1.0 ± 0.7 and 1.3 ± 1.0 mU/L; mean \pm SD of T_3 varied between 1.6 ± 0.2 and 1.8 ± 0.3 nmol/L; mean \pm SD of free T_4 varied between 16.2 ± 2.8 and 17.1 ± 4.0 pmol/L). Clinical chemistry safety indexes showed no pathological changes.

Local tolerability at the injection site was good in most patients. Transient (1–2 days), mild to moderate pain at the injection site was occasionally reported by 10, swelling by 4, and rubor by 1 patient, but did not cause discontinuation of the study medication.

Glucose tolerance

One patient was treated with glibenklamide for diabetes mellitus at entry into the study. HbA_{1c} increased initially from 6.3% to 7.8%, but returned to pretreatment values after a period of intensified drug and diet treatment and suppression of GH. Another patient who had diabetic glucose tolerance but normal HbA_{1c} at the start of the study showed no change in glucose tolerance during treatment with Sandostatin LAR. In a third patient oral glucose tolerance deteriorated, but her HbA_{1c} remained within the normal range. Two patients dropped out of the study before reevaluation of oral glucose tolerance. In the remaining patients, mean values of fasting glucose, peak glucose, and 2-h glucose values during oral glucose tolerance testing were similar before and during im treatment with Sandostatin LAR (Fig. 5). Their corresponding HbA_{1c} (mean \pm SD before treatment, $5.7 \pm 0.5\%$; after 12 months, $5.4 \pm 0.5\%$; after 18 months, $5.6 \pm 0.5\%$) also remained unchanged during treatment. Insulin and C peptide values obtained during oral glucose tolerance testing after 12 and 18 months of treatment were similar.

Discussion

These present results confirm and expand previous experience with Sandostatin LAR in acromegalic patients known to be sensitive to octreotide. In our patients, 20 mg of the drug reduced GH and IGF-I levels consistently when given at 4-week intervals during long term treatment. As seen during the initial studies with the drug (4), increasing the dosage to 30 mg had no obvious additional effect on GH suppression, but provided a further decrease in IGF-I levels. This might be the result of a direct effect of octreotide on the production of IGF-I and IGF-binding proteins (14, 15) or to more subtle effects on GH secretion not detected by the present study. Forty milligrams of the drug had no additional effect on GH or IGF-I compared to 30 mg. Although the effect of Sandostatin LAR was not improved after the higher dosage, serum levels of octreotide increased with dosage. During the initial studies we found a prolongation of the duration of GH suppression from 4 weeks to at least 6 weeks when the dosage of Sandostatin LAR was increased from 20 to 30 mg, im (4). This opens the possibility of an individual adjustment of the time interval between the injections when using the higher dosages of Sandostatin LAR, as previously suggested by others (12). However, our study was designed neither to confirm this hypothesis nor to rule out the possibility of an effect of the higher dosages of Sandostatin LAR in the occasional patients. The manufacturer currently recommends a 4-week interval between the injections of Sandostatin LAR regardless of dosage. It has been observed that GH and IGF-I suppression may improve continuously during sc treatment with octreotide three times daily (1, 5). On the other hand, it could be hypothesized that treatment with prolonged release formulations of somatostatin analogs might cause desensitization and escape from effects with time (16). Our data, however, do not support such a hypothesis. We found a stable and consistent suppression of GH and IGF-I during 18 subsequent im injections of Sandostatin LAR.

Octreotide inhibits GH, insulin, and glucagon (17). In acromegaly, many of the actions of excess GH on carbohydrate

TABLE 2. Effects of increasing doses of Sandostatin LAR

Octreotide dosage	GH ($\mu\text{g/L}$)	IGF-I ($\mu\text{g/L}$)	Octreotide (ng/L)	Symptom score
1				
Basal (n = 9)	10.1 ± 10.0	922 ± 342		5.6 ± 2.8
20 mg	2.9 ± 3.1^a	$481 \pm 326^{a,b}$	1098 ± 612^b	2.6 ± 2.3^a
30 mg	2.2 ± 2.1^a	$393 \pm 265^{a,b}$	2093 ± 616^b	2.6 ± 2.6^a
2				
Basal (n = 7)	11.8 ± 9.0	1147 ± 104		6.1 ± 3.4
30 mg	3.2 ± 1.6^a	574 ± 209^a	2001 ± 732^b	1.7 ± 1.7^a
40 mg	3.1 ± 1.6^a	588 ± 198^a	2443 ± 867^b	1.5 ± 1.2^a

Dose-response data during Sandostatin LAR therapy in patients with acromegaly. Values are the mean \pm SD.

^a $P < 0.05$ vs. baseline.

^b $P < 0.05$ vs. lower dose.

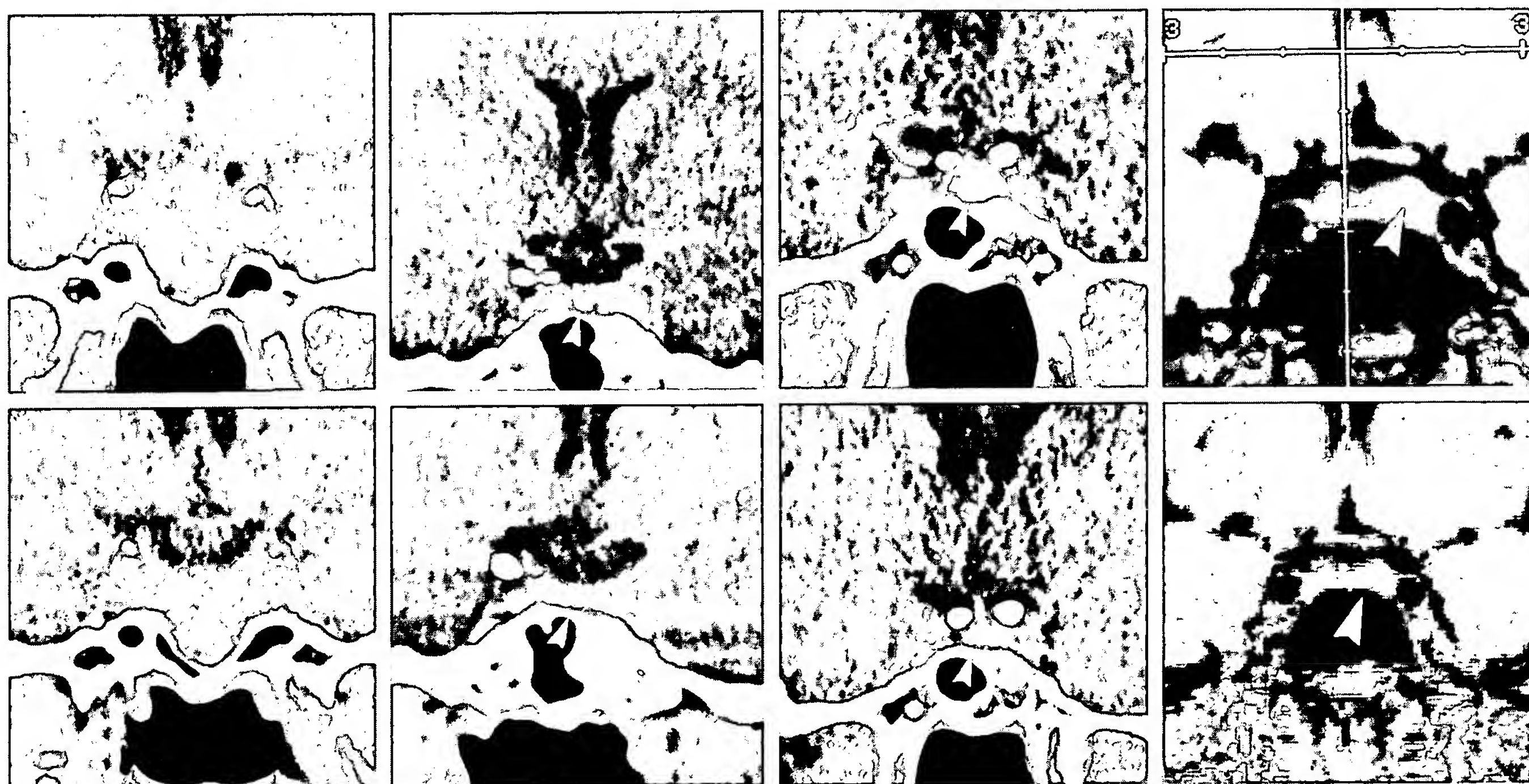


FIG. 4. Basal (upper panel) and final (lower panel) CT (patients 11, 13, and 14) or MRI (patient 12) scans showing the pituitary gland and surrounding structures of the four patients with tumor shrinkage during Sandostatin LAR treatment. The arrow indicates a pathological change in the anatomy of the pituitary gland.

metabolism are antagonistic to insulin (18). Successful octreotide treatment of acromegals improves insulin sensitivity and counterbalances the inhibition of insulin secretion (19). Both beneficial effects on glucose tolerance in acromegals with glucose intolerance as well as impairment of metabolic control during octreotide treatment are described (3, 20–22). We found only minor changes in glucose metabolism in the nondiabetic acromegalic patients during treatment with Sandostatin LAR. In one patient with noninsulin-dependent diabetes mellitus at entry into the study, a transient impairment of metabolic control was seen.

Our findings of tumor size reduction in 4 of the 14 patients during treatment is in agreement with previous reports during sc treatment with Sandostatin (1–3, 5–7, 9–11). Radiological identification of a pituitary tumor in patients previously treated by surgery or irradiation may be difficult, and we were unable to find any effect of Sandostatin LAR on tumor size in such patients. However, in accordance with the results of preoperative sc treatment of acromegalic patients

with octreotide (8) and previous experience with Sandostatin LAR (4, 12), we found tumor size reduction in all previously untreated patients during im treatment with Sandostatin LAR.

Although most patients had gastrointestinal complaints initially, a noticeable reduction of this side-effect occurred with time. This observation is in agreement with reports on long term sc treatment with octreotide (9–11). One of our patients acquired vitamin B12 deficiency during treatment. A decrease in vitamin B12 levels in acromegalic patients during sc treatment with octreotide has previously been reported (23). In the present study only one patient developed asymptomatic gallstones after 18 months of treatment. This is in accordance with previous reports on sc treatment with octreotide (1–3), in which 4–18% of the subjects developed gallstones during long term treatment. The significant loss of scalp hair seen in two of our patients was also previously reported during sc treatment with octreotide for acromegaly (24).

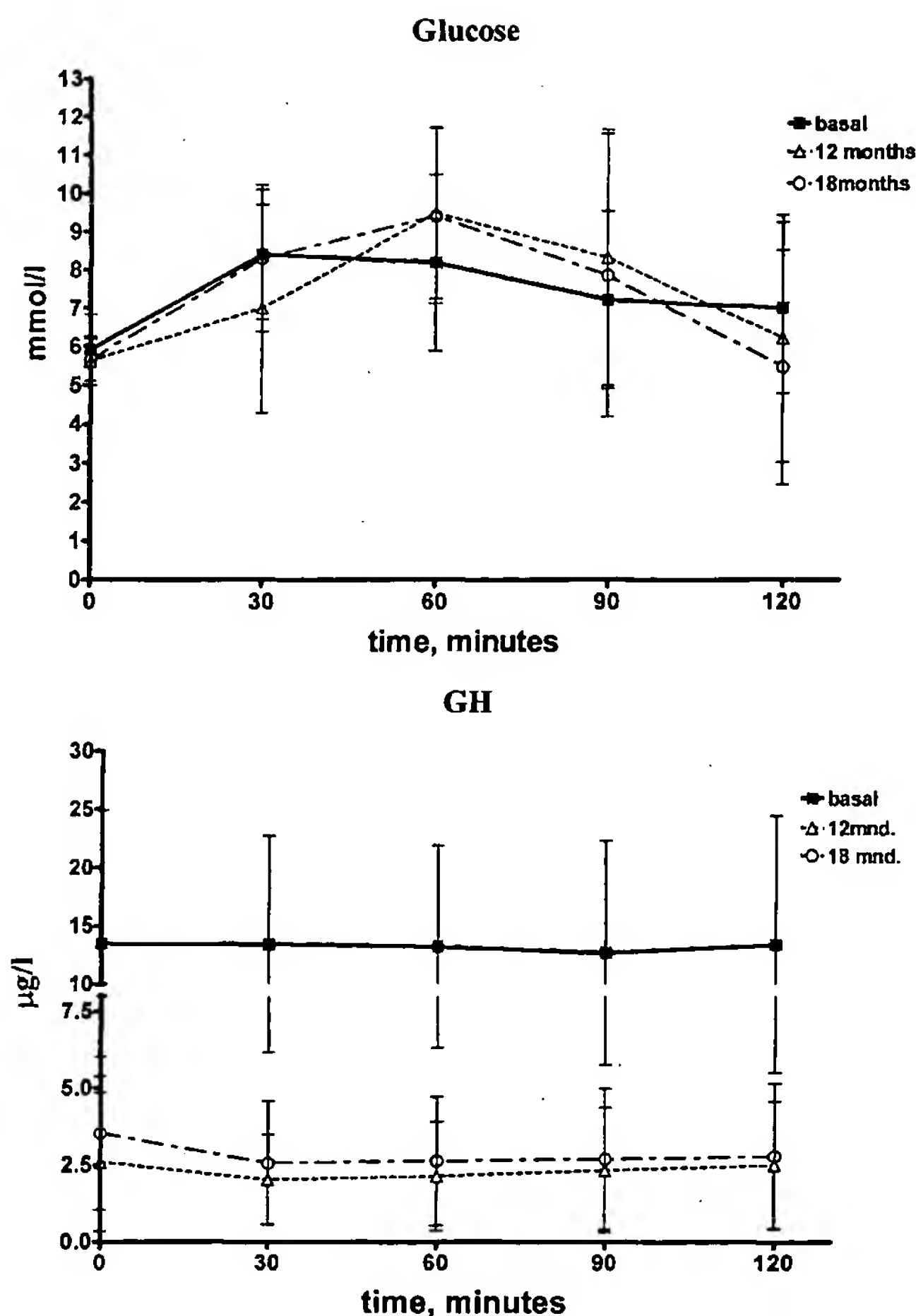


FIG. 5. Glucose and GH measured during oral glucose tolerance tests (OGTT) performed before study start and after the twelfth and eighteenth injection of Sandostatin Lar im. All measurements are mean and standard deviations of values obtained in nine patients. Three patients who discontinued the study prematurely and two patients with pathological OGTT before study (see text) are not included.

In summary, long term treatment with Sandostatin LAR effectively ameliorates symptoms and reduces GH and IGF-I consistently in octreotide-sensitive acromegalic patients. Our experience after more than 24 months of treatment substantiate this impression. In previously untreated patients it also reduces pituitary tumor size. The drug is well tolerated during long term treatment.

Sandostatin LAR may well be the future medical treatment of choice for acromegalic patients.

Acknowledgments

We are grateful to Elisabeth Rambøl, Trine O. Larsen, and Inger Jansen, registered nurses, for valuable assistance during this study. Kristin Godang, Kari Kvamsdal, and Sian Thomas provided technical help. Sian Thomas, H.N.D., and Thor Ueland, technician, assisted in preparing the manuscript.

References

- Vance ML, Harris AG. 1991 Long-term treatment of 189 acromegalic patients with the somatostatin analog octreotide. Results of the internal multicenter acromegaly study group. *Arch Intern Med*. 151:1573-1578.
- Ezzat S, Snyder PJ, Young WF, et al. 1992 Octreotide treatment of acromegaly: a randomized, multicenter study. *Ann Intern Med*. 117:711-718.
- Arosio M, Macchelli S, Rossi CM, et al. 1995 Effects of the treatment with octreotide in acromegalic patients—a multicenter Italian study. *Eur J Endocrinol*. 133:430-439.
- Fløgstad A.K., Halse J, Haldorsen T, Lancranjan I, Jervell J. 1995 Sandostatin® LAR® in acromegalic patients: a dose-response study. *J Clin Endocrinol Metab*. 80:3601-3607.
- Lamberts SWJ, Uitterlinden P, Del Pozo E. 1987 SMS 201-995 induces a continuous decline in circulating growth hormone and somatostatin-C levels during therapy of acromegalic patients for over two years. *J Clin Endocrinol Metab*. 65:703-710.
- Christensen C, Weeke J, Ørskov H, et al. 1987 Continuous subcutaneous pump infusion of somatostatin analogue SMS 201-995 versus subcutaneous injection schedule in acromegalic patients. *Clin Endocrinol (Oxf)*. 27:297-306.
- Barkan AL, Kelch RP, Hopwood NJ, Beitins IZ. 1988 Treatment of acromegaly with the long-acting somatostatin analog 201-995. *J Clin Endocrinol Metab*. 66:16-23.
- Barkan AL, Lloyd RV, Chandler WF, et al. 1988 Preoperative treatment of acromegaly with long-acting somatostatin analog SMS 201-995: shrinkage of invasive pituitary macroadenomas and improved surgical remission rate. *J Clin Endocrinol Metab*. 67:1040-1048.
- Tauber JP, Babin Th, Tauber MT, et al. 1989 Long term effect of continuous subcutaneous infusion of the somatostatin analog octreotide in the treatment of acromegaly. *J Clin Endocrinol Metab*. 68:917-924.
- James RA, Chatterjee S, White MC, Hall K, Møller N, Kendall-Taylor P. 1989 Continuous infusion of octreotide in acromegaly. *Lancet*. 2:1083-1087.
- Sassolas G, Harris AG, James-Deidier A, The French SMS 201-995 Acromegaly Study Group. 1990 Long term effect of incremental doses of the somatostatin analog SMS 201-995 in 58 acromegalic patients. *J Clin Endocrinol Metab*. 71:391-397.
- Stewart PM, Kane FK, Stewart SE, Lancranjan I, Sheppard MC. 1995 Depot long-acting somatostatin analog (Sandostatin® LAR®) is an effective treatment for acromegaly. *J Clin Endocrinol Metab*. 80:3267-3272.
- Fløgstad AK, Halse J, Grass P, et al. 1994 A comparison of octreotide, bromocriptine or a combination of both drugs in acromegaly. *J Clin Endocrinol Metab*. 79:461-465.
- Flyvbjerg A, Jørgensen KD, Marshall SM, Ørskov H. 1991 Inhibitory effect of octreotide on growth hormone-induced IGF-I generation and ovarian growth in the hypophysectomized rats. *Am J Physiol*. 260:568-574.
- Ezzat S, Ren SG, Braunstein GD, Melmed S. 1992 Octreotide stimulates insulin-like growth factor-binding protein-1: a potential pituitary independent mechanism for action. *J Clin Endocrinol Metab*. 75:1459-1463.
- Lamberts SWJ, Verleun T, Zuidervijk JM, Oosterom R. 1987 The effect of the somatostatin analog SMS 201-995 on normal growth hormone secretion in the rat. A comparison with the effect of bromocriptine on normal prolactin secretion. *Acta Endocrinol (Copenh)*. 115:196.
- Bauer W, Briner U, Doeppner R, et al. 1982 A very potent and selective octapeptide analog of somatostatin with prolonged action. *Life Sci*. 31:1133-1140.
- Davidson MB. 1987 Effects of GH on carbohydrate and lipid metabolism. *Endocr Rev*. 8:115-131.
- Breider M, Pinzer T, Wildbrett J, Bornstein SR, Hanefeld M. 1995 Long-term effect of octreotide in acromegaly on insulin resistance. *Horm Metab Res*. 27:226-230.
- Halse J, Harris AG, Kvistborg A, et al. 1990 A randomized study of SMS 201-995 versus bromocriptine treatment in acromegaly: clinical and biochemical effects. *J Clin Endocrinol Metab*. 79:461-465.
- Ho KK, Jenkins AB, Furler SM, Borkman M, Chrisholm DJ. 1992 Impact of octreotide, a long-acting somatostatin analogue, on glucose tolerance and insulin sensitivity in acromegaly. *Clin Endocrinol (Oxf)*. 36:271-279.
- Koop BL, Harris AG, Ezzat S. 1994 Effect of octreotide on glucose tolerance in acromegaly. *Eur J Endocrinol*. 130:581-586.
- Plöckinger U, Dienemann D, Quabbe HJ. 1990 Gastrointestinal side-effects of octreotide during long term treatment of acromegaly. *J Clin Endocrinol Metab*. 71:1658-1662.
- Nakauchi Y, Kumon Y, Yamasaki H, Tahara K, Kurisaka M, Hashimoto K. 1995 Scalp hair loss caused by octreotide in a patient with acromegaly: a case report. *Endocr J*. 42:385-389.